IMPACT OF RANOLAZINE ON INFLAMMATORY, THROMBOGENIC, LIPOGENIC, BIOMARKERS IN WOMEN WITH ANGINA AND METABOLIC SYNDROME

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RATIONALE

More than 5 million women are living with angina today compared to 4 million men. More women than men are affected with the metabolic syndrome (MBS) – a clustering of several cardiovascular risk factors such as pre-hypertension, dyslipidemia and disturbed glucose metabolism associated with central adiposity. Prior studies show an intimate connection of insulin resistance to an increased state of inflammation, thrombogenicity and atherogenicity. The prevalence of these risk factor clusters is high in women, and notoriously higher in ethnic minority groups. In apparently healthy individuals, MBS leads to an increased risk of cardiovascular disease and type 2 diabetes. In those with pre-existing cardiovascular disease (CVD), MBS is associated with advanced vascular damage and poorer outcomes. MBS appears to impart a higher risk in women relative to men in either of these groups. Women tend to have more chronic anginal symptoms than men after myocardial infarction (MI), percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG). The reason for this gender difference in angina and MBS is unclear. To date, data are limited regarding the interaction of the MBS components with the pathobiology of angina in women or men.

Given the favorable effects of ranolazine on angina and on glycemic control, the following study proposes to assess the effect of ranolazine on; 1-relavant biomarkers of cardiometabolic risk in women with MBS and chronic stable angina (CSA) and 2-angina frequency.

Currently, specific treatment and recommendations are lacking for subjects with MBS and CSA, and each component of the syndrome is generally treated independently. When these subjects are assessed in the context of stable ischemia; it may be

particularly important to seek agents that may offer overlapping benefit. Thus, the proposed study intends to elucidate the associations of these cardiometabolic markers and help generate mechanistic hypothesis to better understand their complex interplay in this group of women

HYPOTHESIS

Ranolazine positively alters cardiometabolic markers in woman with CSA.

Ranolazine reduces angina frequency in women with MBS and CSA.

PUPOSE OF STUDY

- Evaluate the ability of ranolazine to favorably modify thrombogenic, inflammatory, lipogenic, oxidative stress and hormonal biomarkers in a relatively short period of time in a group of ethnically diverse women with CSA and MBS.
- Evaluate the ability of ranolazine to favorably decrease angina frequency and nitroglycerine use in a relatively short time in a group of ethnically diverse women with CSA and MBS.
- Obtain preliminary data to use in the design of a larger study to help elucidate the mechanisms underlying the link between angina, metabolic, hormonal, inflammatory, thrombogenic abnormalities that underline angina symptoms in women with MBS.

SPECIFIC OBJECTIVES

- To determine the impact of ranolazine on selected thrombogenic, lipogenic, hormonal and inflammatory biomarkers in women with angina and MBS.
- To determine the impact of ranolazine in decreasing angina frequency in women with MBS.

PATIENT CHARACTERISTICS

ELIGIBILITY

Ages Eligible for Study: 30 Years or older.

Gender: female

Number: 40 eligible women with MBS, coronary artery disease (CAD) and CSA.

CRITERIA

Inclusion Criteria:

Patients with CSA (any anginal symptoms in the last 3 months) on evidence based adequate therapy.

Evidence of stable CAD by any of these:

MI, PCI or CABG >30 days prior to enrollment.

OR

Angiography showing >= 50% stenosis in major vessel, branch or bypass graft > 30 days of enrollment.

OR

Abnormal stress nuclear myocardial perfusion imaging study or dobutamine stress echocardiography where the decision has been to treat medically and where angina has remained stable for ≥ 3 months.

Evidence of MBS: As defined by ATP III criteria

i.e **3/5** of following

Abdominal circumference **F > 88cm (35in),** M> 102 com (40in)

Hypertriglyceridemia ≥ 150 mg/dL

HDL **F < 50 mg/dl**

M < 40 mg/dl

Blood pressure ≥ 130/85

Fasting Glucose ≥ 100 mg/dL

For reproductive age women, a negative urine pregnancy test is required if all other inclusion criteria are met.

Exclusion Criteria

Exclusion of patients with contraindications of use of ranolazine, including patients on CYP3A4 inducers/potent inhibitors, and patients with liver cirrhosis.

Exclusion of patients with CrCl < 30 mL/min.

Limit dose of ranolazine to 500mg BID in patients on concurrent diltiazem/verapamil.

Limit concurrent simvastatin to 20 mg/day.

Limit concurrent metformin to 1700 mg/day.

Additional Exclusion

Patients with variable – inconsistent symptoms.

Patients with unstable CAD and revascularization within 30 days of enrolment.

Patients who have known severe liver disease.

Patients already receiving maximal ranolazine therapy for more than 4 weeks.

Presence of diabetes (AIC≥ 6.5 and /or on insulin therapy or anti-diabetic medication other than metformin) unstable hypothyroidism, active infection, active cancer (or ongoing chemotherapy and/or radiation within a year who are not on remission) and/or recent major surgery or illness.

Patients with any contraindication to ranolazine (see above).

Women of reproduction age are excluded if they are planning to become pregnant in the next 6-12 months after randomization.

Patients who are pregnant or lactating

Documented allergic reaction to ranolazine in the past.

Unexplained prolongation of the QTc > 500 milliseconds.

Current or planned co-administration of moderate CYP3A inhibitors (eg, diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products) is not a full contraindication, if meet inclusion criteria otherwise, these patients could be accepted in trial but dose will be limited to 500 mg BID as stated previously.

Current or planned co-administration of strong CYP3A inhibitors (eg, ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir) OR strong CYP3A inducers (eg, rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's Wort) is a contraindication.

SCREENING AND RECRUITMENT

Estimated **8-10 months to enroll 40 patients – on average 5 per month.**

Study site: University of Florida – Cardiology Division. Patients will be recruited from the cardiology outpatient clinic at Shands – Jacksonville Cardiovascular Center and The Women's Cardiovascular Health Program at Emerson Cardiology Associates and North Side Cardiovascular clinical practice (satellite offices of UF cardiology outpatient services).

Estimated time frame to conduct study: **Up to 12 months after last patient enrolled**

STUDY PROTOCOL

After assessment of screened candidates, a total of 40 eligible patients will be randomized in a 1:1 ratio to receive double blind treatment with either ranolazine or matching placebo.

> Patients assigned to ranolazine would start with **500 mg BID** and be force titrated to **1 gram po BID** after 3 weeks. Down titration would only be allowed for side effects. This would be on top of all standard medical therapy. Therapy will continue to the end of protocol (24 weeks).

Patients assigned to the placebo arm would start with **500 mg matching placebo tablet BID** and be force titrated to **1 gram matching placebo tablet BID** after 3 weeks. Down titration would only be allowed for side effects (if reported). This would be on top of all standard medical therapy.

Eligible subject (those with MBS and CSA) will be evaluated at the time of randomization and thereafter in **clinic for follow up visits at 3 wks, 6 wks, 12 wks, 18 wks, 24 wks.** Blood samples for (approximately 9 teaspoons) **biomarkers analysis will be obtained at randomization, and at 12 and 24 weeks** after randomization in all patients. All specified blood markers will be tested in this group as noted in the table of scheduled events. These subjects will follow identical testing schedule.

SAFETY AND TOLERABILITY MONITORING

Basic chemistry and Liver function testing will be done at time of randomization only to ensure normal electrolytes and liver function.

All patients will receive follow up phone calls at 3 week intervals from randomization to completion of study to assess for possible adverse clinical events, side effects (dizziness, headache, constipation, nausea, etc.) and overall compliance. An emergency contact telephone will be provided for participants to report any concerns or possible drug reactions at any time during the study. A Medical Monitor, independent of the study, will be assigned to monitor study data on an ongoing basis making sure that continuing the investigation in its current format remains appropriate, on both safety and scientific grounds.

SCHEDULE OF EVENTS

EVENT	SCREENING LABS***	Week 0 BASE LINE	Week 3 +/- 3 days	Week 6 +/- 3 days	Week 9 +/- 3 days	Week 12 +/- 3 days	Week 15 +/- 3 days	Week 18 +/- 3 days	Week 21 +/- 3 days	Week 24 +/- 3 days

Consenting/ Clinic visit		**X**	**X**	**X**		**X**		**X**		**X**
Blood Pressure/HR		**X**		**X**		**X**		**X**		**X**
Abdomen Circumference		**X**				**X**				**X**
Pregnancy Test (if required)		**X**								
Basic Chemistry Panel	**X**	**X**								
Liver Profile (LFTS)	**X**	**X**								
Myeloperoxidase		**X**				**X**				**X**
Relaxin-2		**X**				**X**				**X**
ADMA		**X**				**X**				**X**
PAI-l		**X**				**X**				**X**
Hs-CRP/s-ICAM and s-VCAM		**X**				**X**				**X**
Leptin		**X**				**X**				**X**
Adiponectin		**X**				**X**				**X**
FLP/ ApoA and Apo Bs		**X**				**X**				**X**
FG		**X**				**X**				**X**
FI		**X**				**X**				**X**
HgbA1C		**X**				**X**				**X**
Pro-BNP		**X**				**X**				**X**
**Drug Dosing Forced uptitration to 1 gram BID			**X**							
*Telephone Follow-Up		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

*Telephone follow-up every 3 weeks.

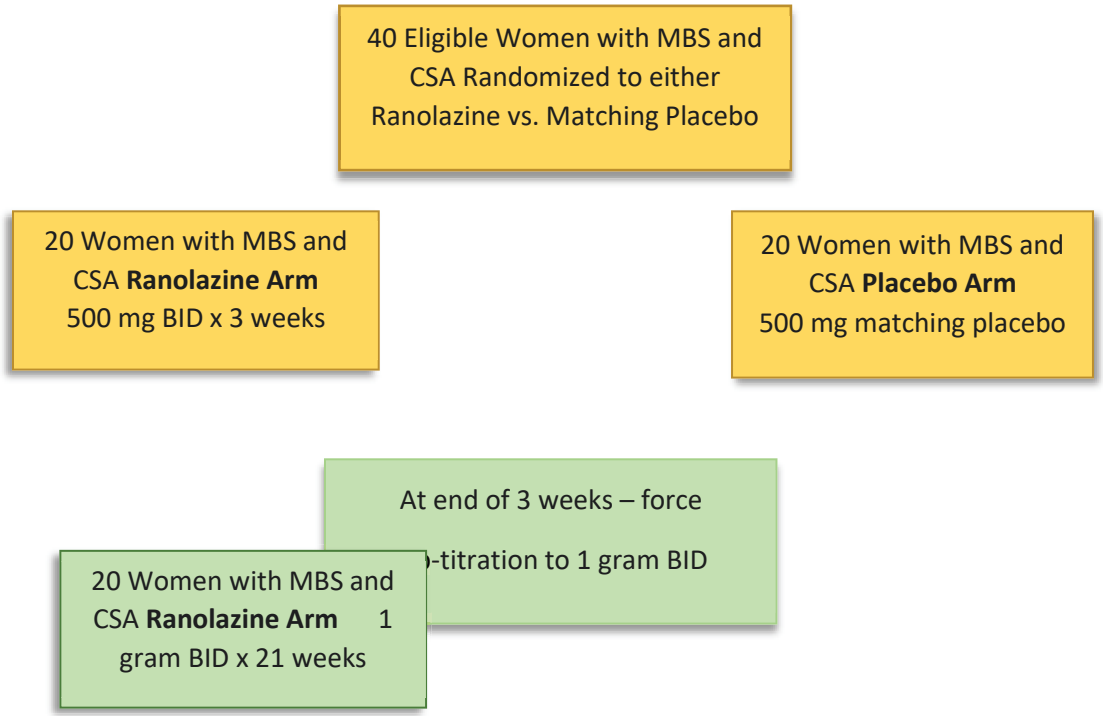
**Forced uptitration of ranolazine to 1 gram BID (or matching placebo) unless contraindicated.

***Labs available within 90 days prior of week 1 may be used as screening labs.

STUDY DESIGN

Local pilot trial, double blind, parallel group trial. Six months duration for all 40 patients recruited. Study is estimated to be completed within **12 months** after last patient enrolled.

Impact of Ranolazine on Cardiac Biomarkers in Women with MBS and CSA



20 Women with MBS and CSA **Placebo Arm** 1 gram x 21 weeks

END POINTS

Primary Endpoints

- Percentage change from baseline in metabolic markers.
- Percentage change from baseline in lipogenic parameters.
- Percentage change from baseline in thrombogenic markers.
- Percentage change from baseline in oxidative stress markers.
- Percentage change from baseline in inflammatory markers.
- Percentage change from baseline in novel – new hormonal markers.

Secondary Endpoints

- Proportion of patients no longer meeting MS classification at end of randomized treatment arm.
- Decrease in frequency of anginal symptoms

SAMPLE SIZE AND DATA ANALYSIS

There is limited to no data on the effect of ranolazine on markers proposed in this study, thus sample size power calculation on this study is of limited value and not accurate. The sample selection is for purposes of hypothesis generation.

The effect of ranolazine on tested blood markers will be evaluated using student t-test and analysis of variance ifdistribution is normal and by nonparametric method if distribution is not normal. Correlation analysis of tested markers will be performed and

subsequent regression analysis allowing independence of the association between thrombo-inflammatory-metabolic-lipogenic profile and drug effect to be performed.

BLOOD

MARKERS TO BE MEASURED

1) **Inflammatory:**
   - **a)** *Hs-CRP*
   - **b)** *Adhesion molecules*
     - **i)** *sICAM-1*
     - **ii)** *sVCAM*
2) **Metabolic:**
   - **a)** *Fasting Glucose (FG)*
   - **b)** *Fasting Insulin (FI)*
   - **c)** *Hgb A1C*
   - **d)** *Leptin*
   - **e)** *Adiponectin*
3) **Thrombogenic:**
   - **a)** *PAI-I*
4) **Lipogenic**
   - **a)** *TC (HDL, LDL, Direct, Trig)*
   - **b)** *Apoliprotein (Apo A1 & Apo B)*
5) **Oxidative Stress**
   - **a)** *Myeloperoxidase*
6) **Other: Novel-New-Hormonal**
   - **a)** *Relaxin-2*
   - **b)** *ADMA (Asymmetric Dimethylarginine)*
   - **c)** *Pro-BNP*

MANAGEMENT OF CLINICAL SUPPLIES

This will be a double-blind study. Study drugs and placebo are being supplied by Gilead. University of Florida Pharmacy will package and label study supplies. Packages of study drugs will be dispensed according to the instructions provided by University of Florida-UF Health Pharmacy. The treatment each subject will receive will not be disclosed to the Investigator or subjects. The treatment codes will

be maintained by University of Florida-UF Health Jacksonville Pharmacy. The blind will be broken when there is a clear life-threatening emergency.

RISKS

The study drug, in very rare circumstances, may cause a change in the heart rhythm called prolongation of QT interval and this may change the way the heart beats and cause palpitations or dizzy spells. A mild prolongation of the QT interval is expected and is not harmful and has been proven safe in numerous trials (no Black Box warning). The study may cause abdominal discomfort, dyspepsia, dizziness and/or headache. These are uncommon and are reversible, i.e, disappear when the drug is discontinued.

Subjects will be advised to report any unexplained dizzy spells, bradycardia, paresthesia, hypotension, or face edema. The most common reported adverse events with the study drug are mild dizziness, headache, constipation, nausea, asthenia, vertigo, blurred vision, abdominal pain, dyspepsia, vomiting, and anorexia.

Participating subjects will be closely monitored for early identification of those who may be experiencing side effects. If side effects are reported, the subject will be removed from the study and followed closely with continued telephone follow-up and laboratory testing if necessary. No routine tests are recommended for ranolazine otherwise.

Pregnancy is a contraindication for the use of the study drug as there are reports of adverse fetal effects but no controlled human studies are available. Eligible women of reproductive age who wish to participate are required to be on birth control to insure the highest level of safety. The birth control methods used by each individual patient are entirely their individual choice.

Temporary discomfort, slight bruising at the site of venipuncture, infection, lightheadedness, and fainting may occur with study blood testing.

BENEFITS

Subjects assigned to the treatment arm will likely experience relief of angina symptoms and will be given a choice to continue with treatment after discussing individually with their primary care physician with caution of not un-blinding study prematurely. There is no guarantee that subjects will benefit by participating in this study. Women may benefit in the future from the results of this study. Participating subjects will be contributing to the understanding of the interaction of angina and the metabolic syndrome and how it can be treated.

ALTERNATIVES

The alternative to participating in the study is not to participate. Patients will continue planned medical treatment with their primary health care providers.

PATIENT CONSENT

Each patient will sign a study-specific consent form to serve as a participant in the study. The consent form will comply with all applicable regulations governing the protection of human subjects.

Prior to enrollment, subjects will be provided a copy of the approved consent form for their review. The investigator or authorized member of the study staff will discuss with the subjects the nature of the drug to be administered and the nature of the study, including risks. Subjects will have the opportunity to inquire about details of the study given sufficient time to discuss participation in the study, and to decide whether or not to participate. If they decide to participate, they will be asked to provide a signed informed consent before initiation of any study related procedures. They will be instructed that they are free to withdraw their participation in the study at any time without prejudice. The subjects will be informed of new information that may be relevant to their willingness to continue participation in the study.

CONFIDENTIALITY

Subject names will not be supplied to the sponsor. Only subject numbers and subject initials will be recorded on case report forms. Study documents will be kept in a secure locked office accessible to the study staff only. Study findings/data will be stored on a computer which is password protected and encrypted according to HIPAA regulations. The subjects will be informed that representatives of the sponsor, independent monitors, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

A personal subject identification list (subject numbers with corresponding subject names) will be maintained to enable records to be identified.

COST TO SUBJECT

There is no cost to subject to participate in this study, except for the cost of transportation to the clinic office. The study medication, study-related tests and study visits will be provided free of charge.

PAYMENT TO SUBJECT

Subjects with the MBS who undergo randomization will not receive payment for participating in the study.